CLAIMS

1. (Currently Amended) A method for preparing a steroidal carbothiolic acid or a salt thereof, said method comprises:

A) reacting a steroidal carboxylic acid or a salt thereof with a coupling agent selected from the group consisting of carbodiimide derivatives represented by the following formula:

R_a—N=C=N—R_b

wherein R_a and R_b are the same or different, and each represent an aliphatic, heteroaliphatic, carbocyclic or a heterocyclic group, wherein the group is ~~[all said groups are~~ optionally substituted~~]~~;

alone or in conjunction with a coupling enhancer; and

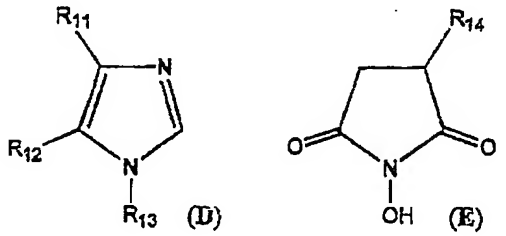
B) reacting the product of step A) with a nucleophilic agent comprising a sulfur atom.

2. (Original) A method according to claim 1 in which the coupling agent is 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC).

3. (Original) A method according to claim 2, in which the coupling agent is the hydrochloride salt of EDC.

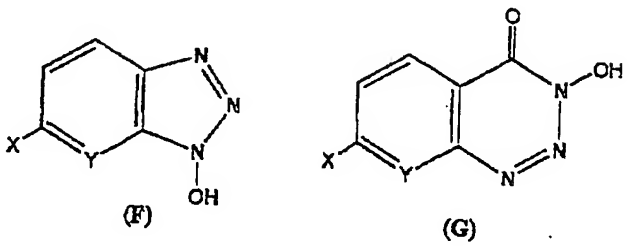
4. (Currently Amended) A method according to claim 1 ~~any of the preceding claims~~, in which the coupling enhancer is selected from the group consisting of:

A) a heterocyclic ring ~~containing one or two nitrogen atoms, said ring being optionally substituted; such as a compound~~ of formula (D) or formula (E),



wherein R_{11} and R_{12} can be the same or different, and each represent a hydrogen atom or a cyano group; R_{13} represent a hydrogen atom or an alkyl group; and R_{14} represent a hydrogen atom or a salt of a sulfonic acid ~~such as sodium sulfonate [-S(=O)(=O)-O⁻Na⁺]~~; and

B) an unsaturated 5-6 membered heterocyclic ring ~~fused to an aromatic- or heteroaromatic ring in which the said heterocyclic ring contains three nitrogen atoms, said rings being optionally substituted, such as a compound~~ of formula (F) or formula (G),



X = H, F, Cl, Br and Y = CH, N, O, S

~~Preferably 6-chloro-hydroxybenzotriasole (6-Cl-HOBt), 7-aza-hydroxybenzotriasole (HOAt), or 3-hydroxy-4-oxo-3,4-dihydro-1,2,3-benzotriazine (Dbht-OH).~~

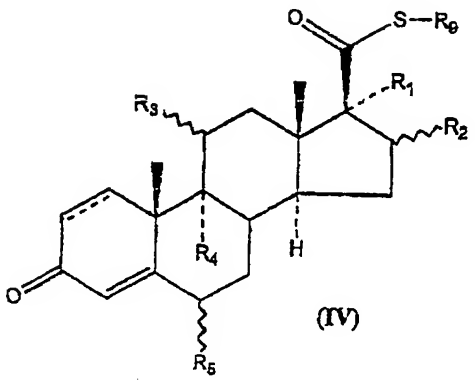
5. (Currently Amended) A method according to claim 1~~any of the preceding claims~~, where the nucleophilic agent comprising a sulfur atom is selected from the group consisting of~~comprising~~:

compounds of formula $[M]^+[SH]^-$ wherein M is a metal such as Li, Na or K; or $[M]^{2+}[S]^{2-}$ wherein M is a metal such as Ca or Mg, the said sulfide salts being optionally hydrated ~~(such as sodium hydrosulfide hydrate)~~; and

an *in situ* generated sulfide salt or a hydrated sulfide salt.

6. (Currently Amended) The method of claim 1~~any of the preceding claims~~, wherein the nucleophilic agent is dissolved in a suitable solvent prior to addition to the reaction mixture, or wherein the nucleophilic agent is added in the form of a solid salt or as a solution of the salt in water, ~~and/or~~ an organic solvent, or a combination thereof.

7. (Currently Amended) A method according to claim 1~~any of the preceding claims~~ for preparing a steroidal carbothioic acid of formula (IV) or a salt thereof

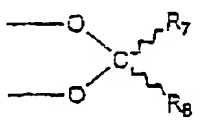


(IV)

wherein the symbol ═ in the 1,2-position represent a single or a carbon-carbon double bond;

R_1 represents a hydrogen atom, a hydroxy- or an alkoxy group~~(such as an optionally substituted C_{1-6} alkoxy)~~ in the *a*-configuration, a group -O-C(=O)-R_6 is an alkyl group~~(such as optionally substituted C_{1-6} alkyl)~~ or an optionally substituted 5-6 membered heterocyclic ring containing either oxygen, nitrogen or sulfur as ring hetero atom~~(such as a furanyl , pyrrolyl or a thiophenyl group)~~;

R_2 represents a hydroxy group, an alkoxy group~~(such as an optionally substituted C_{1-6} alkoxy)~~ in the *n*-configuration, an alkyl group~~(such as an optionally substituted C_{1-6} alkyl)~~ which may be in either the η- or β-configuration, an alkylene group~~(such as an optionally substituted C_{1-4} alkylene having the two free valencies on the same carbon atom preferably methylene)~~. wherein ~~[~~the alkylene group is bound to the steroid nucleus via a double bond.~~]~~ or R_1 and R_2 together represent



where R_7 and R_8 are the same or different and each represent a hydrogen atom or an alkyl group ~~(such as an optionally substituted C_{1-6} alkyl)~~;

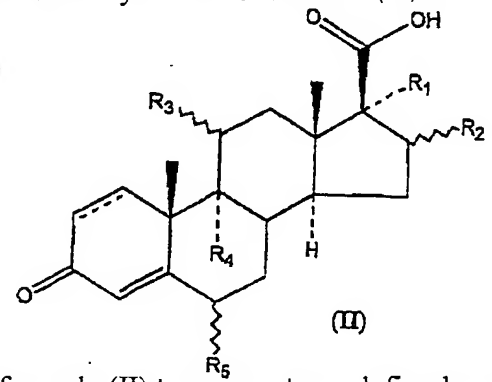
R_3 represent a hydrogen atom, hydroxy-or a protected hydroxy group in either a *α- or β-* configuration or an oxo group ~~(in which case the bond between R_3 and the steroid nucleus is a double bond)~~;

R_4 represents a hydrogen- or a halogen atom or R_3 and R_4 together represent a carbon-carbon bond or an epoxy group in the β-configuration; and

R_5 represents a hydrogen- or a halogen atom in either the α- or β-configuration;

R_9 represents a hydrogen atom or R_9 represent a metal ion ~~[e.g. The moiety $-SR_9$ represents a group of the formal $[-S]^-[M]^+$ wherein M is a metal such as Li, Na or K]~~; the method comprising;

A) reacting a steroidal carboxylic acid of formula (II) or a salt thereof



(II)

in which the substituents of formula (II) have the above defined meaning with a coupling agent alone or in conjunction with an coupling enhancer, followed by the reaction with a nucleophilic agent comprising a sulfur atom; and optionally

B) reacting the product from step A) with an acid.

8. (Currently Amended) The method of claim 1 ~~any of the preceding claims~~, wherein i)

the coupling agent is added before the coupling enhancer, or

the coupling enhancer is added before the coupling agent, and/or wherein ii)

the steroidal carboxylic acid is added to a mixture of the coupling agent and the coupling enhancer, or wherein

a mixture of the coupling agent and the coupling enhancer is added to a steroidal

carboxylic acid, or wherein

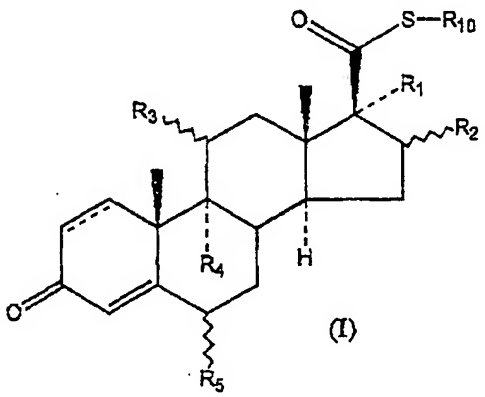
the steroidal carboxylic acid is added to a mixture of the coupling agent and the coupling enhancer in a polar aprotic solvent, preferably DMF or DMA, at elevated temperature.

9. (Currently Amended) A method for preparing a steroidal carbothioate ~~(i.e. the ester of the steroidal carbothioic acid)~~, or a salt thereof, the method comprising;

reacting a steroidal carbothioic acid or a salt thereof~~, which is prepared as defined in any of the preceding claims,~~ with an electrophillic agent.

10. (Currently Amended) A method according to claim 9, in which the electrophillic agent is selected from the group consisting of: C_{1-8} di- or trihaloalkanes~~, preferably a trihalo- or a dihalomethane, such as chlorobromomethane or bromofluoromethane~~.

11. (Currently Amended) A method according to claim 9 ~~or 10~~ for preparing a steroidal carbothioate of formula (I)



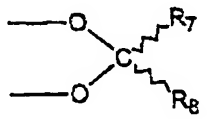
(I)

wherein R_1, R_2, R_3, R_4 and R_5 are ~~defined as in claim 7~~;

R_1 represents a hydrogen atom, a hydroxy- or an alkoxy group in the α-configuration, a group -O-C(=O)-R_6 is an alkyl group or an optionally substituted 5-6 membered heterocyclic ring containing either oxygen, nitrogen or sulfur as ring hetero atom;

R_2 represents a hydrogen atom, a hydroxy group, an alkoxy group in the β-configuration,

an alkyl group which may be in either the α- or β-configuration, an alkylene group, wherein the alkylene group is bound to the steroid nucleus via a double bond, or R_1 and R_2 together represent



where R_7 and R_8 are the same or different and each represent a hydrogen atom or an alkyl group;

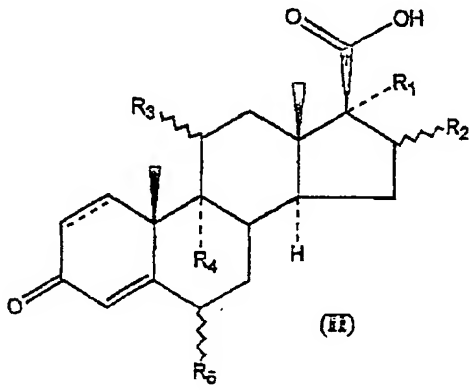
R_3 represent a hydrogen atom, hydroxy-or a protected hydroxy group in either a *α- or β-* configuration or an oxo group;

R_4 represents a hydrogen- or a halogen atom or R_3 and R_4 together represent a carbon-carbon bond or an epoxy group in the β-configuration; and

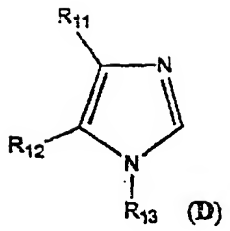
R_5 represents a hydrogen- or a halogen atom in either the α- or β-configuration

and R_{10} represents a $C_{1\,5}$ haloalkyl or an optionally substituted heterocyclic ring, the method comprising:

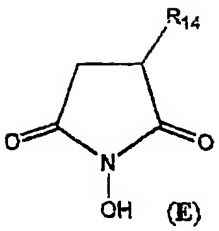
A) reacting a steroidal carboxylic acid of formula (II)



with a coupling agent and a coupling enhancer ~~[such as a compound~~ of formula (D) or formula(E)]



(D)



(E)

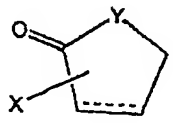
wherein R_{11} and R_{12} independently represent a hydrogen atom or a cyano group (C=N);

R_{12} represent a hydrogen atom or an alkyl group; and

R_{14} represent a hydrogen atom or a moiety of a sulfonic acid~~, such as sodium sulfonate (e.g. The group $-S(=O)(=O)-O^-Na^+$)~~]

B) reacting the product from step A) with a nucleophilic agent comprising sulfur; and

C) reacting the product from step B) with an electrophillic agent ~~[such as a C_{1-6} di- or trihaloalkane, preferably a trihalo- or a dihalomethane such as chlorofluoromethane or bromofluoromethane]~~ or a compound of the following formula;



wherein X=H, F, Cl, or Br and; Y=CH_2, NH, O, or S~~, preferably X=Cl and Y=O~~.

12. (Original) The method of claim 11, wherein the coupling enhancer is selected from the group consisting of: NMI (N-methylimidazole); DCI (4,5-dicyanolmidazole); NHS (N-hydroxysuccinimide); and sulfo-NHS (N-hydroxysulfosuccinimide).

13. (Currently Amended) The method of ~~any of the~~ claims 11~~-12~~, wherein step C) constitutes the *in situ* reaction of the product from step B) with bromofluoromethane to form a

compound of formula (I) wherein R_{10} is a fluoromethyl group~~, such as fluticasone propionate~~.

14. (Currently Amended) The method according to claim 9~~any of the preceding claims~~, in which

at least two subsequent steps are performed *in situ*~~, i.e. without any change or removal of solvents, or isolation of the individual intermediates; and/or~~

the method is conducted as a continuous method;~~ and/or~~

step A), B) and optionally step C) are conducted as a one-pot synthesis without solvent changes~~, and/or~~ are performed at room or elevated temperature, or both; or

a combination of one or more of the foregoing.

15. (Currently Amended) The method of ~~any of the~~ claims 9~~-14~~, wherein an androstane 17β-carboxylic acid is converted to an androstane 17β-carbothioate.

16. (Currently Amended) The method of claim 9~~any of the preceding claims~~, wherein step B) provides ~~an alkali metal salt of the thioic acid, such as~~ a compound of formula (IV), in which the moiety –5-R_5 represent a group of the formula $[-S]^-[M]^+$ wherein M is a metal such as Li, Na or K~~ e.g. S^-Na^+, and the other substituents have the same meaning as defined in claim 7.~~

wherein the symbol ⎓ in the 1,2-position represent a single or a carbon-carbon double bond;

R_1 represents a hydrogen atom, a hydroxy- or an alkoxy group in the *a*-configuration, a group -O-C(=O)-R_6 is an alkyl group or an optionally substituted 5-6 membered heterocyclic ring containing either oxygen, nitrogen or sulfur as ring hetero atom;

R_2 represents a hydrogen atom, a hydroxy group, an alkoxy group in the *n*-configuration, an alkyl group which may be in either the η- or β-configuration, an alkylene group, wherein the alkylene group is bound to the steroid nucleus via a double bond, or R_1 and R_2 together represent

where R_7 and R_8 are the same or different and each represent a hydrogen atom or an alkyl group;

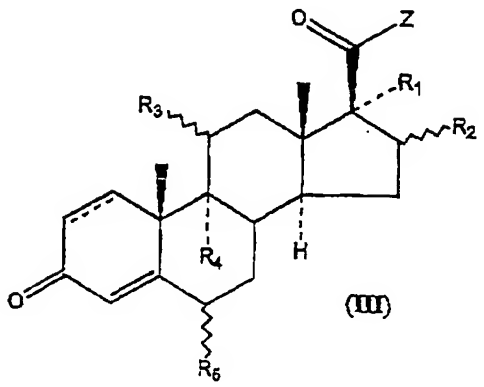
R_3 represent a hydrogen atom, hydroxy-or a protected hydroxy group in either a *α- or β-* configuration or an oxo group;

R_4 represents a hydrogen- or a halogen atom or R_3 and R_4 together represent a carbon-carbon bond or an epoxy group in the β-configuration; and

R_5 represents a hydrogen- or a halogen atom in either the α- or β-configuration;

R_9 represents a hydrogen atom or R_9 represent a metal ion.

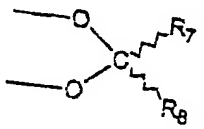
17. (Currently Amended) A compound of the formula (III) and salts and solvates thereof



(III)

~~W~~wherein R_1 represents a hydrogen atom, a hydroxy- or an alkoxy group in the *α*-configuration, a group -O-C(=O)-R_6 is an alkyl group or an optionally substituted 5-6 membered heterocyclic ring containing either oxygen, nitrogen or sulfur as ring hetero atom;

R_2 represents a hydrogen atom, a hydroxy group, an alkoxy group in the *n*-configuration, an alkyl group which may be in either the η- or β-configuration, an alkylene group, wherein the alkylene group is bound to the steroid nucleus via a double bond, or R_1 and R_2 together represent



where R_7 and R_8 are the same or different and each represent a hydrogen tom or an alkyl group;

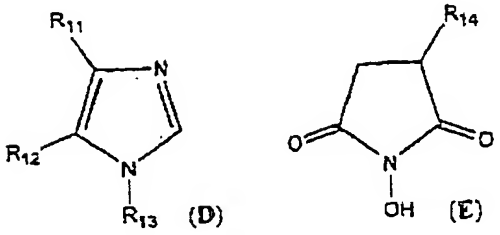
R_3 represent a hydrogen atom, hydroxy-or a protected hydroxy group in either a *α- or β-*configuration or an oxo group;

R_4 represents a hydrogen- or a halogen atom or R_3 and R_4 together represent a carbon-carbon bond or an epoxy group in the β-configuration; and

R_5 represents a hydrogen- or a halogen atom in either the α- or β-configuration; and

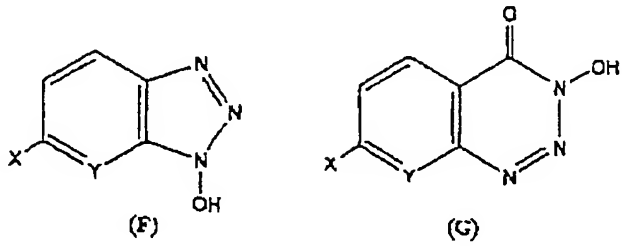
Z represent the structural moiety resulting from the reaction between the steroidal carboxylic acid of formula (II) and a coupling agent ~~(preferably EDC)~~, followed by a coupling

enhancer selected from the group consisting of the compounds of formulas (D); (E); (F); and (G):



(D) (E)

wherein R_{11} and R_{12} independently represent a hydrogen atom or a cyano group; R_{13} represent a hydrogen atom or a methyl group; and R_{14} represent a hydrogen atom or a moiety of a sulfonic acid~~, such as sodium sulfonate [i.e. The group $-S(=O)(=O)-O^-Na^+$]~~,



(F) (G)

X - H, F, Cl, Br and Y - CH, N, O, S

with the proviso that:

when the coupling enhancer is a compound of formula (F), X can not represent H when Y represents CH:

when the coupling enhancer is a compound of formula (D), R_{11} and R_{12} can not both represent H when R_1 in formula III represents DH; and

when the coupling enhancer is a compound of formula (E), R_{14} can not represent H when R_1 in formula III represents H;

and with the further proviso that

succinlmidyl-9υ-fluoro-11β, 17α-dihydroxy-16α-methyl-3-oxoandrosta-1,4-diene-17β-carboxylate;

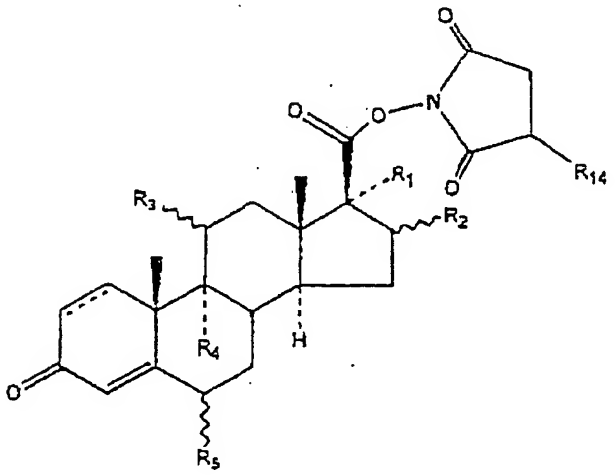
17α-hydroxy-4-androsten-3-one-17β-carboxylic acid N-hydroxysuccinimide ester;

N-hydroxysuccinimidyl-9-fluoro-16α-methyl-11β, 17-dihydroxy-3-oxo-1,4-androstadiene-17β-carboxyester;

N-hydroxysuccinimide ester of dexamethasone-17β-carboxylic acid; and 1-[(9-fluoro-11β-hydroxy-16β-methyl-3-oxo-17α-propionylaxyandrosta-1,4-dien-17β-yi)carbonyl]imidazol are disclaimed.

18. (Currently Amended) The compound of claim 17, wherein at least one of R_{11} and R_{12} is a cyano group (C=N), ~~and/or~~ R_{13} is a hydrogen atom, ~~and/or~~ formula (D) is NMI (N-methylimidazole) or DCI (4,5-dicyano-imidazole), ~~and/or~~ formula (E) is NHS (N-hydroxysuccinimide) or sulfo-NHS (N-hydroxysulfosuccinimide), or a combination comprising one or more of the foregoing.

19. (Currently Amended) The compound of claim 17, having the formula:



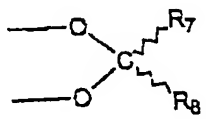
~~In which the substituents have the same meaning as defined in claim 17, and salts and solvates thereof,~~ with the proviso that R_{14} can not represent H when R_1 represents H.

20.(Currently Amended) A compound of the formula (VI) and salts and solvates thereof

~~wherein R_1, R_2, R_3, R_4 and R_5 are defined as in claim 7; and R_a and R_b are defined as in claim 1;~~

R_1 represents a hydrogen atom, a hydroxy- or an alkoxy group ~~(such as an optionally substituted C_{1-6} alkoxy)~~ in the *a*-configuration, a group -O-C(=O)-R_6 is an alkyl group ~~(such as optionally substituted C_{1-5} alkyl)~~ or an optionally substituted 5-6 membered heterocyclic ring containing either oxygen, nitrogen or sulfur as ring hetero atom ~~(such as a furanyl-, pyrrolyl- or a thiophenyl group)~~;

R_2 represents a hydrogen atom, a hydroxy group, an alkoxy group ~~(such as an optionally substituted C_{1-6} alkoxy)~~ in the *n*-configuration, an alkyl group ~~(such as an optionally substituted C_{1-6} alkyl)~~ which may be in either the η- or β-configuration, an alkylene group ~~(such as an optionally substituted C_{1-6} alkylene having the two free valencies on the same carbon atom preferably methylene)~~. wherein ~~[~~the alkylene group is bound to the steroid nucleus via a double bond~~,]~~ or R_1 and R_2 together represent



where R_7 and R_8 are the same or different and each represent a hydrogen tom or an alkyl group ~~(such as an optionally substituted C_{1-6} alkyl)~~;

R_3 represent a hydrogen atom, hydroxy-or a protected hydroxy group in either a *α- or β-* configuration or an oxo group ~~(in which case the bond between R_3 and the steroid nucleus is a double bond)~~;

R_4 represents a hydrogen- or a halogen atom or R_3 and R_4 together represent a carbon-carbon bond or an epoxy group in the β-configuration; and

R_5 represents a hydrogen- or a halogen atom in either the α- or β-configuration,

wherein R_a and R_b are the same or different, and each represent an aliphatic, heteroaliphatic, carbocyclic or a heterocyclic group;

with the proviso that 1-(3-dimethylamino-propyl)-3-ethyl-carbodiimide-6α, 9υ-difluoro-11β-hydroxy-16α, 17α-isopropylidenedioxy-3-oxo-androsta-1,4-diene-17β-carboxylate is disclaimed.

21-23. (Cancelled).